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This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

Docket No. P51337P

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TITLE OF THE INVENTION (280 characters max)
NF-KB INHIBITORS

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ENCLOSED APPLICATION PARTS (check all that apply)

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<input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge filing fees and credit Deposit Account No. 19-2570	PROVISIONAL FILING FEE AMOUNT (\$)	\$160.00
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Respectfully submitted,
Signature:

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Date:

4/11/02

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☐ Additional inventors are being named on separately numbered sheets attached hereto.

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PATENT TRADEMARK OFFICE

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NF- κ B INHIBITORS**FIELD OF THE INVENTION**

- This invention relates in general to a method of inhibiting pathological activation of the transcription factor NF- κ B (nuclear factor- κ B) using
- 5 aminothiophene compounds. Such methods are particularly useful for treating diseases in which activation of NF- κ B is implicated. More specifically, these methods may be used for inhibiting IKK- β (I κ B kinase- β) phosphorylation of I κ B (inhibitory protein κ B)-which prevents subsequent degradation and activation of NF- κ B dimers. Such methods are useful in the treatment of a variety of diseases
- 10 associated with NF- κ B activation including inflammatory and tissue repair disorders; particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease) osteoarthritis; osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage; autoimmune diseases including systemic lupus
- 15 erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome, Ataxia
- 20 Telangiectasia.

BACKGROUND OF THE INVENTION

- Recent advances in scientific understanding of the mediators involved in acute and chronic inflammatory diseases and cancer have led to new strategies in the search for effective therapeutics. Traditional approaches include direct target
- 25 intervention such as the use of specific antibodies, receptor antagonists, or enzyme inhibitors. Recent breakthroughs in the elucidation of regulatory mechanisms involved in the transcription and translation of a variety of mediators have led to increased interest in therapeutic approaches directed at the level of gene transcription.

Nuclear factor κ B (NF- κ B) belongs to a family of closely related dimeric transcription factor complexes composed of various combinations of the Rel/NF- κ B family of polypeptides. The family consists of five individual gene products in mammals, RelA (p65), NF- κ B1 (p50/p105), NF- κ B2 (p49/p100), c-Rel, and RelB, all of which can form hetero- or homodimers. These proteins share a highly homologous 300 amino acid "Rel homology domain" which contains the DNA binding and dimerization domains. At the extreme C-terminus of the Rel homology domain is a nuclear translocation sequence important in the transport of NF- κ B from the cytoplasm to the nucleus. In addition, p65 and cRel possess potent transactivation domains at their C-terminal ends.

The activity of NF- κ B is regulated by its interaction with a member of the inhibitor I κ B family of proteins. This interaction effectively blocks the nuclear localization sequence on the NF- κ B proteins, thus preventing migration of the dimer to the nucleus. A wide variety of stimuli activate NF- κ B through what are likely to be multiple signal transduction pathways. Included are bacterial products (LPS), some viruses (HIV-1, HTLV-1), inflammatory cytokines (TNF α , IL-1), environmental and oxidative stress and DNA damaging agents. Apparently common to all stimuli however, is the phosphorylation and subsequent degradation of I κ B. I κ B is phosphorylated on two N-terminal serines by the recently identified I κ B kinases (IKK- α and IKK- β). Site-directed mutagenesis studies indicate that these phosphorylations are critical for the subsequent activation of NF- κ B in that once phosphorylated the protein is flagged for degradation via the ubiquitin-proteasome pathway. Free from I κ B, the active NF- κ B complexes are able to translocate to the nucleus where they bind in a selective manner to preferred gene-specific enhancer sequences. Included in the genes regulated by NF- κ B are a number of cytokines and chemokines, cell adhesion molecules, acute phase proteins, immunoregulatory proteins, eicosanoid metabolizing enzymes and anti-apoptotic genes.

It is well-known that NF- κ B plays a key role in the regulated expression of a large number of pro-inflammatory mediators including cytokines such as TNF, IL-1 β , IL-6 and IL-8, cell adhesion molecules, such as ICAM and VCAM, and

inducible nitric oxide synthase (iNOS). Such mediators are known to play a role in the recruitment of leukocytes at sites of inflammation and in the case of iNOS, may lead to organ destruction in some inflammatory and autoimmune diseases.

The importance of NF- κ B in inflammatory disorders is further strengthened by studies of airway inflammation including asthma, in which NF- κ B has been shown to be activated. This activation may underlie the increased cytokine production and leukocyte infiltration characteristic of these disorders. In addition, inhaled steroids are known to reduce airway hyperresponsiveness and suppress the inflammatory response in asthmatic airways. In light of the recent findings with regard to glucocorticoid inhibition of NF- κ B, one may speculate that these effects are mediated through an inhibition of NF- κ B.

Further evidence for a role of NF- κ B in inflammatory disorders comes from studies of rheumatoid synovium. Although NF- κ B is normally present as an inactive cytoplasmic complex, recent immunohistochemical studies have indicated that NF- κ B is present in the nuclei, and hence active, in the cells comprising rheumatoid synovium. Furthermore, NF- κ B has been shown to be activated in human synovial cells in response to stimulation with TNF- α or IL-1 β . Such a distribution may be the underlying mechanism for the increased cytokine and eicosanoid production characteristic of this tissue. See Roshak, A. K., et al., *J. Biol. Chem.*, **271**, 31496-31501 (1996). Expression of IKK- β has been shown in synoviocytes of rheumatoid arthritis patients and gene transfer studies have demonstrated the central role of IKK- β in stimulated inflammatory mediator production in these cells. See Aupperle et al. *J. Immunology* 1999. 163:427-433 and Aupperle et al. *J. Immunology* 2001;166:2705-11. More recently, the intra-articular administration of a wild type IKK- β adenoviral construct was shown to cause paw swelling while intra-articular administration of dominant-negative IKK- β inhibited adjuvant-induced arthritis in rat. See Tak et al. *Arthritis and Rheumatism* 2001; 44:1897-1907.

The NF- κ B/Rel and I κ B proteins are also likely to play a key role in neoplastic transformation and metastasis. Family members are associated with cell transformation *in vitro* and *in vivo* as a result of overexpression, gene amplification,

gene rearrangements or translocations. In addition, rearrangement and/or amplification of the genes encoding these proteins are seen in 20-25% of certain human lymphoid tumors. Further, NF- κ B is activated by oncogenic ras, the most common defect in human tumors and blockade of NF- κ B activation inhibits ras mediated cell transformation. In addition, a role for NF- κ B in the regulation of apoptosis has been reported, strengthening the role of this transcription factor in the regulation of tumor cell proliferation. TNF, ionizing radiation and DNA damaging agents have all been shown to activate NF- κ B which in turn leads to the upregulated expression of several anti-apoptotic proteins. Conversely, inhibition of NF- κ B has been shown to enhance apoptotic-killing by these agents in several tumor cell types. As this likely represents a major mechanism of tumor cell resistance to chemotherapy, inhibitors of NF- κ B activation may be useful chemotherapeutic agents as either single agents or adjunct therapy. Recent reports have implicated NF- κ B as an inhibitor of skeletal cell differentiation as well as a regulator of cytokine-induced muscle wasting (Guttridge et al. *Science*; 2000; 289: 2363-2365.) further supporting the potential of NF- κ B inhibitors as novel cancer therapies.

Several NF- κ B inhibitors are described in C. Wahl, et al. *J. Clin. Invest.* 101(5), 1163-1174 (1998), R. W. Sullivan, et al. *J. Med. Chem.* 41, 413-419 (1998), J. W. Pierce, et al. *J. Biol. Chem.* 272, 21096-21103 (1997)

The marine natural product hymenialdisine is known to inhibit NF- κ B. Roshak, A., et al., *JPET*, 283, 955-961 (1997). Breton, J. J and Chabot-Fletcher, M. C., *JPET*, 282, 459-466 (1997).

Additionally, patent applications have been filed on indole and benzimidazole inhibitors of the IKK complex, see DE 19928424 and WO200130774, and the natural products staurosporine, quercetin, K252a and K252b have been shown to be IKK- β inhibitors, see Peet, G. W. and Li, J. J. *Biol. Chem.*, 274, 32655-32661 (1999) and Wisniewski, D., et al., *Analytical Biochem.* 274, 220-228 (1999).

U.S. Patent No. 3,963,750 describes the preparation of certain aminothiophenes.

SUMMARY OF THE INVENTION

The present invention involves novel compounds and novel methods of inhibiting the activation transcription factor NF- κ B using the present compounds.

5 An object of the present invention is to provide a method for treating diseases which may be therapeutically modified by altering the activity of transcription factor NF- κ B.

Accordingly, in the first aspect, this invention provides a pharmaceutical composition comprising a compound according to Formula I.

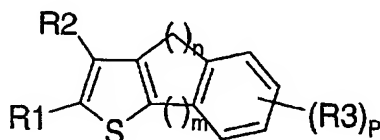
10 In another aspect, this invention provides a method of treating diseases in which the disease pathology may be therapeutically modified by inhibiting phosphorylation and subsequent degradation of I κ B by IKK- β .

In still another aspect, this invention provides a method of treating diseases in which the disease pathology may be therapeutically modified by inhibiting
15 pathological activation of NF- κ B.

In a particular aspect, this invention provides methods for treating a variety of diseases associated with NF- κ B activation including inflammatory and tissue repair disorders, particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease) osteoarthritis,
20 osteoporosis and fibrotic diseases, dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage; autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease,
25 cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome and Ataxia Telangiectasia

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are selected from Formula (I) herein below:



(I)

wherein:

R₁ represents NR₄R₅;

10 R₂ represents CONH₂ or SO₂NH₂;

R₃ is selected from the group consisting of halogen, C₁₋₄alkyl, NH₂, CF₃, OCF₃, O-alkyl, S-alkyl, CN, CHO, SO₂-alkyl, (CH₂)_qNR₇R₈, O-(CH₂)_qNR₇R₈ and NO₂;

R₄ represents C₁₋₄alkyl;

R₅ represents CONHR₆;

15 R₆ is selected from the group consisting of hydrogen, alkyl and aryl;

R₇ represents C₁₋₄alkyl;

R₈ represents C₁₋₄alkyl or R₇ and R₈ taken together form a 5-7 member ring;

m is 0, 1, 2 or 3;

n is 0, 1, 2, or 3

20 p is 1, 2 or 3 and

q is 1, 2, 3 or 4.

Preferred compounds useful in the present invention include:

2-Amino-4H-indeno[1,2b]thiophene-3-carboxylic acid amide;

2-Ureido-4H-indeno[1,2b]thiophene-3-carboxylic acid amide;

25 2-Amino-4,5-dihydro-naphtho[2,1-b]thiophene-3-carboxylic acid amide; and

2-Ureido-4,5-dihydro-naphtho[2,1-b]thiophene-3-carboxylic acid amide.

This invention provides methods for treating a variety of diseases associated with NF-κB activation including inflammatory and tissue repair disorders; particularly

rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease) osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage; autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome, and Ataxia Telangiectasia.

DEFINITIONS

The present invention includes all hydrates, solvates, complexes and prodrugs of the compounds of this invention. Prodrugs are any covalently bonded compounds, which release the active parent, drug according to Formulas I and II *in vivo*. If a chiral center or another form of an isomeric center is present in a compound of the present invention, all forms of such isomer or isomers, including enantiomers and diastereomers, are intended to be covered herein. Inventive compounds containing a chiral center may be used as a racemic mixture, an enantiomerically enriched mixture, or the racemic mixture may be separated using well-known techniques and an individual enantiomer may be used alone. In cases in which compounds have unsaturated carbon-carbon double bonds, both the *cis* (Z) and *trans* (E) isomers are within the scope of this invention. In cases wherein compounds may exist in tautomeric forms, such as keto-enol tautomers, each tautomeric form is contemplated as being included within this invention whether existing in equilibrium or predominantly in one form.

The meaning of any substituent at any one occurrence in Formula I or any subformula thereof is independent of its meaning, or any other substituent's meaning, at any other occurrence, unless specified otherwise.

As used herein, "alkyl" refers to an optionally substituted hydrocarbon group joined by single carbon-carbon bonds and having 1-6 carbon atoms joined together.

The alkyl hydrocarbon group may be linear, branched or cyclic, saturated or

unsaturated. Substituents on optionally substituted alkyl are selected from the group consisting of aryl, OH, O-alkyl, CO, halogen, CF₃, and OCF₃.

As used herein, "aryl" refers to an optionally substituted aromatic group with at least one ring having a conjugated pi-electron system, containing up to two
5 conjugated or fused ring systems. Aryl includes carbocyclic aryl, and biaryl groups, all of which may be optionally substituted. Substituents are selected from the group consisting of halogen, C₁₋₄ alkyl, NH₂, OCF₃, CF₃, O-alkyl, S-alkyl, CN, CHO, SO₂-alkyl and NO₂.

As used herein, "heteroaryl" refers to an optionally substituted aromatic
10 group with at least one ring having a conjugated pi-electron system, containing up to two conjugated or fused ring systems and 1-3 heteroatoms selected from O, S and N. Heteroaryl includes carbocyclic heteroaryl, aryl-heteroaryl and biheteroaryl groups, all of which may be optionally substituted. Preferred aryl include phenyl and naphthyl. More preferred aryl include phenyl. Preferred substituents are selected
15 from the group consisting of halogen, C₁₋₄ alkyl, NH₂, OCF₃, CF₃, O-alkyl, S-alkyl, CN, CHO, SO₂-alkyl and NO₂. Examples of heteroaryl rings included pyrrole, furan, thiophene, indole, isoindole, benzofuran, isobenzofuran, benzothiphenene, pyridine, quinoline, isoquinoline, quinolizine, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, pyridazine, pyrimidine, and pyrazine.

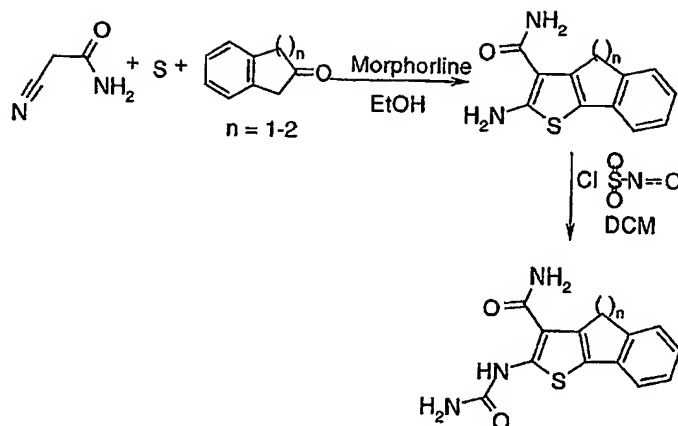
20 As used herein "halogen" refers to include F, Cl, Br, and I.

METHODS OF PREPARATION

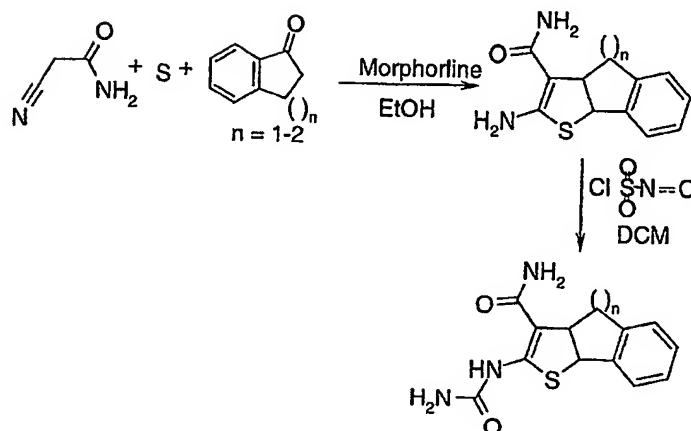
General Preparation:

The general preparation of the aminothiophene analogs is shown in Schemes
25 1-2. Morpholine is added to a stirred solution of cyanoacetamide, sulfur, and cyclic ketone in absolute ethanol. The resulting solution is stirred at room temperature or up to 60°C overnight. The solvent is then removed under *vacuo* and the residue is taken up into ethyl acetate, washed by water and brine, dried over anhydrous magnesium sulfate, filtered and concentrated under *vacuo* to give a dark brown solid.
30 The product is then usually purified by chromatography to give the desired product.

Scheme 1



Scheme 2



The following Experimentals are intended to be illustrative only and not limiting in any way.

Example 1

Preparation of 2-Amino-4H-indeno[1,2b]thiophene-3-carboxylic acid amide trifluoroacetate

Morpholine (1 mL) was added dropwise to a stirred solution of cyanoacetamide (0.84 g, 0.01 mol), sulfur (0.36, 0.012 mol), and 2-indanone (1.32 g, 0.01 mmol) in absolute ethanol (5 mL). The resulting solution was stirred at 60 °C overnight. The solvent was then removed under vacuo and the residue was taken up into ethyl acetate (10 mL), washed by water (2 x 10 mL) and brine (10 mL), dried over anhydrous magnesium sulfate, filtered and concentrated under vacuo to give a

dark brown solid. The product was then purified on Gilson preparative HPLC (YMC HPLC column 50 X 20 mm I.D., s-5 μ m, 120 Å; gradient elution, 0.1%TFA in acetonitrile:0.1% aqueous TFA, 10:90 to 90:10, 10 min) to give the title compound as a brown solid (100 mg, 0.435 mmol, 4.3% yield). ESMS m/z: 231

5 [M+H]⁺.

Example 2

Preparation of 2-Ureido-4H-indeno[1,2b]thiophene-3-carboxylic acid amide
Chlorosulfonyl isocyanate (0.025 g, 0.17 mL) was added dropwise to a

10 stirred solution of 2-amino-4H-indeno[1,2b]thiophene-3-carboxylic acid amide trifluoroacetate (0.040 g, 0.17 mmol) in dry dichloromethane (2 mL). The resulting reaction mixture was stirred under nitrogen for 30 min. Water (0.5 mL) was then added to the reaction mixture and the reaction mixture was allowed to stir an additional 10 minutes before the solvent was removed under vacuo. The residue was

15 then purified on Gilson preparative HPLC (YMC HPLC column 50 X 20 mm I.D., s-5 μ m, 120 Å; gradient elution, 0.1%TFA in acetonitrile: 0.1% aqueous TFA, 10:90 to 90:10, 10 min) to give title compound as brown solid (0.020 g, 0.435 mmol, 43.5% yield). ESMS m/z: 274 [M+H]⁺.

20

Example 3

Preparation of 2-Amino-4,5-dihydro-naphtho[2,1-d]thiophene-3-carboxylic acid amide
The title compound was prepared by the same procedure as Example 1

25 except that 2-indanone was replaced with beta-tetralone to give the above titled compound as a brown solid (60 % pure by LC-MS). ESMS m/z: 245 [M+H]⁺.

Example 4

30 **Preparation of 2-Ureido-4,5-dihydro-naphtho[2,1-b]thiophene-3-carboxylic acid amide**
The title compound was prepared by the same procedure as Example 2 except 2-amino-4H-indeno[1,2b]thiophene-3-carboxylic acid amide was replaced

with 2-amino-4,5-dihydro-naphtho[1,2-d]thiophene-3-carboxylic acid amide to give the above titled compound as a brown solid. ESMS m/z : 288 $[M+H]^+$.

5 This invention provides a pharmaceutical composition, which comprises a compound according to Formula, I and a pharmaceutically acceptable carrier, diluent or excipient. Accordingly, the compounds of Formula I may be used in the manufacture of a medicament. Pharmaceutical compositions of the compounds of Formula I prepared as hereinbefore described may be formulated as solutions or lyophilized powders for parenteral administration. Powders may be reconstituted by
10 addition of a suitable diluent or other pharmaceutically acceptable carrier prior to use. The liquid formulation may be a buffered, isotonic, aqueous solution. Examples of suitable diluents are normal isotonic saline solution, standard 5% dextrose in water or buffered sodium or ammonium acetate solution. Such formulation is especially suitable for parenteral administration, but may also be used
15 for oral administration or contained in a metered dose inhaler or nebulizer for insufflation. It may be desirable to add excipients such as polyvinylpyrrolidone, gelatin, hydroxy cellulose, acacia, polyethylene glycol, mannitol, sodium chloride or sodium citrate.

Alternately, these compounds may be encapsulated, tableted or prepared in
20 an emulsion or syrup for oral administration. Pharmaceutically acceptable solid or liquid carriers may be added to enhance or stabilize the composition, or to facilitate preparation of the composition. Solid carriers include starch, lactose, calcium sulfate dihydrate, terra alba, magnesium stearate or stearic acid, talc, pectin, acacia, agar or gelatin. Liquid carriers include syrup, peanut oil, olive oil, saline and water.
25 The carrier may also include a sustained release material such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies but, preferably, will be between about 20 mg to about 1 g per dosage unit. The pharmaceutical preparations are made following the conventional techniques of pharmacy involving milling, mixing, granulating, and compressing,
30 when necessary, for tablet forms; or milling, mixing and filling for hard gelatin capsule forms. When a liquid carrier is used, the preparation will be in the form of a

syrup, elixir, emulsion or an aqueous or non-aqueous suspension. Such a liquid formulation may be administered directly p.o. or filled into a soft gelatin capsule.

For rectal administration, the compounds of this invention may also be combined with excipients such as cocoa butter, glycerin, gelatin or polyethylene glycols and molded into a suppository.

The methods of the present invention include topical inhaled and intracolonic administration of the compounds of Formula I. By topical administration is meant non-systemic administration, including the application of a compound of the invention externally to the epidermis, to the buccal cavity and instillation of such a compound into the ear, eye and nose, wherein the compound does not significantly enter the blood stream. By systemic administration is meant oral, intravenous, intraperitoneal and intramuscular administration. The amount of a compound of the invention (hereinafter referred to as the active ingredient) required for therapeutic or prophylactic effect upon topical administration will, of course, vary with the compound chosen, the nature and severity of the condition being treated and the animal undergoing treatment, and is ultimately at the discretion of the physician

While it is possible for an active ingredient to be administered alone as the raw chemical, it is preferable to present it as a pharmaceutical formulation. The active ingredient may comprise, for topical administration, from 0.01 to 5.0 wt% of the formulation.

The topical formulations of the present invention, both for veterinary and for human medical use, comprise an active ingredient together with one or more acceptable carriers therefor and optionally any other therapeutic ingredients. The carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of where treatment is required such as: liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active

ingredient in a suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container, which is then sealed and sterilized by autoclaving, or maintaining
5 at 90-100 C for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily
10 solution include glycerol, diluted alcohol and propylene glycol.

Lotions according to the present invention include those suitable for application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may
15 also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by
20 mixing the active ingredient in finely divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy basis. The basis may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap, a mucilage, an oil of natural origin such as almond, corn, arachis, castor or
25 olive oil, wool fat or its derivatives, or a fatty acid such as stearic or oleic acid together with an alcohol such as propylene glycol or macrogols. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surface active agent such as sorbitan esters or polyoxyethylene derivatives thereof. Suspending agents such as natural gums, cellulose derivatives or in organic
30 materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

UTILITY OF THE PRESENT INVENTION

The compounds of Formula I are useful as inhibitors of the IKK-beta kinase phosphorylation of I κ B and as such are inhibitors of NF- κ B activation. The present method utilizes compositions and formulations of said compounds, including pharmaceutical compositions and formulations of said compounds.

The present invention particularly provides methods of treatment of diseases associated with inappropriate NF- κ B activation, which methods comprise administering to an animal, particularly a mammal, most particularly a human in need thereof one or more compounds of Formula I. The present invention particularly provides methods for treating inflammatory and tissue repair disorders, particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease) osteoarthritis, osteoporosis and fibrotic diseases; dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage, autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome and Ataxia Telangiectasia.

For acute therapy, parenteral administration of one or more compounds of Formula I is useful. An intravenous infusion of the compound in 5% dextrose in water or normal saline, or a similar formulation with suitable excipients, is most effective, although an intramuscular bolus injection is also useful. Typically, the parenteral dose will be about 0.01 to about 50 mg/kg; preferably between 0.1 and 20 mg/kg, in a manner to maintain the concentration of drug in the plasma at a concentration effective to inhibit IKK-beta and therefore activation of NF- κ B. The compounds are administered one to four times daily at a level to achieve a total daily dose of about 0.4 to about 80 mg/kg/day. The precise amount of a compound used in the present method which is therapeutically effective, and the route by which such compound is

best administered, is readily determined by one of ordinary skill in the art by comparing the blood level of the agent to the concentration required to have a therapeutic effect.

The compounds of Formulas I may also be administered orally to the patient, in a manner such that the concentration of drug is sufficient to inhibit IKK-beta and therefore activation of NF- κ B or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered at an oral dose of between about 0.1 to about 50 mg/kg in a manner consistent with the condition of the patient. Preferably the oral dose would be about 0.5 to about 20 mg/kg.

The compounds of Formulas I may also be administered topically to the patient, in a manner such that the concentration of drug is sufficient to inhibit IKK-beta and therefore activation of NF- κ B or to achieve any other therapeutic indication as disclosed herein. Typically, a pharmaceutical composition containing the compound is administered in a topical formulation of between about 0.01% to about 5% w/w.

No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The ability of the compounds described herein to inhibit the activation of NF- κ B is clearly evidenced in their ability to inhibit the phosphorylation of the N-terminal fragment of I κ B- α by IKK- β (see Table 1 for examples). These compounds also block the degradation of I κ B- α and the nuclear translocation of NF- κ B in human monocytes and other mammalian cells upon activation of the cells with a pro-inflammatory stimuli (e.g., TNF- α , LPS, etc.). In addition these compounds inhibit pro-inflammatory mediator production from LPS-stimulated human monocytes and stimulated human primary synovial fibroblasts. The utility of the present NF- κ B inhibitors in the therapy of diseases is premised on the importance of NF- κ B activation in a variety of diseases.

NF- κ B plays a key role in the regulated expression of a large number of pro-inflammatory mediators including cytokines such as TNF, IL-1 β , IL-6 and IL-8 (Mukaida *et al.*, 1990; Liberman and Baltimore, 1990; Matsusaka *et al.*, 1993), cell

adhesion molecules, such as ICAM and VCAM (Marui *et al.*, 1993; Kawai *et al.*, 1995; Ledebur and Parks, 1995), and inducible nitric oxide synthase (iNOS) (Xie *et al.*, 1994; Adcock *et al.*, 1994). (Full reference citations are at the end of this section). Such mediators are known to play a role in the recruitment of leukocytes at sites of inflammation and in the case of iNOS, may lead to organ destruction in some inflammatory and autoimmune diseases (McCartney-Francis *et al.*, 1993; Kleemann *et al.*, 1993).

Evidence for an important role of NF- κ B in inflammatory disorders is obtained in studies of asthmatic patients. Bronchial biopsies taken from mild atopic asthmatics show significant increases in the number of cells in the submucosa staining for activated NF- κ B, total NF- κ B, and NF- κ B-regulated cytokines such as GM-CSF and TNF α compared to biopsies from normal non-atopic controls (Wilson *et al.*, 1998). Furthermore, the percentage of vessels expressing NF- κ B immunoreactivity is increased as is IL-8 immunoreactivity in the epithelium of the biopsy specimens (Wilson *et al.*, 1998). As such, inhibition of IL-8 production through the inhibition of NF- κ B, as has been demonstrated by these compounds would be predicted be beneficial in airway inflammation.

Recent studies suggest that NF- κ B may also play a critical role in the pathogenesis of inflammatory bowel disease (IBD). Activated NF- κ B is seen in colonic biopsy specimens from Chron's disease and ulcerative colitis patients (Ardite *et al.*, 1998; Rogler *et al.*, 1998; Schreiber *et al.*, 1998). Activation is evident in the inflamed mucosa but not in uninfamed mucosa (Ardite *et al.*, 1998; Rogler *et al.*, 1998) and is associated with increased IL-8 mRNA expression in the same sites (Ardite *et al.*, 1998). Furthermore, corticosteroid treatment strongly inhibits intestinal NF- κ B activation and reduces colonic inflammation (Ardite *et al.*, 1998; Schreiber *et al.*, 1998). Again, inhibition of IL-8 production through the inhibition of NF- κ B, as has been demonstrated by these compounds would be predicted be beneficial in inflammatory bowel disease.

Animal models of gastrointestinal inflammation provide further support for NF- κ B as a key regulator of colonic inflammation. Increased NF- κ B activity is

observed in the lamina propria macrophages in 2,4,6,-trinitrobenzene sulfonic acid (TNBS)-induced colitis in mice with p65 being a major component of the activated complexes (Neurath *et al.*, 1996; Neurath and Pettersson, 1997). Local administration of p65 antisense abrogates the signs of established colitis in the treated animals with no signs of toxicity (Neurath *et al.*, 1996; Neurath and Pettersson, 1997). As such, one would predict that small molecule inhibitors of NF- κ B would be useful in the treatment of IBD.

Further evidence for a role of NF- κ B in inflammatory disorders comes from studies of rheumatoid synovium. Although NF- κ B is normally present as an inactive cytoplasmic complex, recent immunohistochemical studies have indicated that NF- κ B is present in the nuclei, and hence active, in the cells comprising human rheumatoid synovium (Handel *et al.*, 1995; Marok *et al.*, 1996; Sioud *et al.*, 1998) and in animal models of the disease (Tsao *et al.*, 1997). The staining is associated with type A synoviocytes and vascular endothelium (Marok *et al.*, 1996). Furthermore, constitutive activation of NF- κ B is seen in cultured synoviocytes (Roshak *et al.*, 1996; Miyazawa *et al.*, 1998) and in synovial cell cultures stimulated with IL-1 β or TNF α (Roshak *et al.*, 1996; Fujisawa *et al.*, 1996; Roshak *et al.*, 1997). Thus, the activation of NF- κ B may underlie the increased cytokine production and leukocyte infiltration characteristic of inflamed synovium. The ability of these compounds to inhibit NF- κ B and thereby inhibit the production of pro-inflammatory mediators (e.g. cytokines and prostanoids) by these cells would be predicted to yield benefit in rheumatoid arthritis.

Biological Assays:

The compounds of this invention may be tested in one of several biological assays to determine the concentration of compound, which is required to have a given pharmacological effect.

NF- κ B activity may also be measured in an electrophoretic mobility shift assay (EMSA) to assess the presence of NF- κ B protein in the nucleus. The cells of interest are cultured to a density of 1×10^6 /mL. The cells are harvested by centrifugation, washed in PBS without Ca²⁺ and Mg²⁺ and resuspended in PBS with

- Ca²⁺ and Mg²⁺ at 1x10⁷ cells/mL. To examine the effect of compound on the activation of NF-κB, the cell suspensions are treated with various concentrations of drug or vehicle (DMSO, 0.1%) for 30 min. at 37 °C prior to stimulation with TNF-α (5.0 ng/mL) for an additional 15 min. Cellular and nuclear extracts are prepared
- 5 follows. Briefly, at the end of the incubation period the cells (1x10⁷ cells) are washed 2x in PBS without Ca²⁺ and Mg²⁺. The resulting cell pellets are resuspended in 20 uL of Buffer A (10 mM Hepes (pH 7.9), 10 mM KCl, 1.5 mM MgCl₂, 0.5 mM dithiothreitol (DTT) and 0.1% NP-40) and incubated on ice for 10 min. The nuclei are pelleted by microcentrifugation at 3500 rpm for 10 min at 4 °C. The resulting
- 10 supernatant was collected as the cellular extract and the nuclear pellet was resuspended in 15 uL Buffer C (20 mM Hepes (pH 7.9), 0.42 M NaCl, 1.5mM MgCl₂, 25% glycerol, 0.2 mM EDTA, 0.5 mM DTT, and 0.5 mM phenylmethylsulphonyl fluoride (PMSF)). The suspensions are mixed gently for 20 min at 4 °C then microcentrifuged at 14,000 rpm for 10 min at 4 °C. The
- 15 supernatant is collected and diluted to 60 uL with Buffer D (20mM Hepes (pH 7.9), 50 mM KCl, 20% glycerol, 0.2 mM EDTA, 0.5 mM DTT, and 0.5 mM PMSF). All samples are stored at -80 °C until analyzed. The protein concentration of the extracts is determined according to the method of Bradford (Bradford, 1976) with BioRad reagents.
- 20 The effect of compounds on transcription factor activation is assessed in an electrophoretic mobility shift assay (EMSA) using nuclear extracts from treated cells as described above. The double stranded NF-κB consensus oligonucleotides (5'-AGTTGAGGGGACTTTCCCAGGC-3') are labelled with T₄ polynucleotide kinase and [γ-³²P]ATP. The binding mixture (25 uL) contains 10 mM Hepes-NaOH (pH
- 25 7.9), 4 mM Tris-HCl (pH 7.9), 60 mM KCl, 1 mM EDTA, 1 mM dithiothreitol, 10% glycerol, 0.3 mg/mL bovine serum albumin, and 1 ug poly(dI-dC)•poly(dI-dC). The binding mixtures (10 ug nuclear extract protein) are incubated for 20 min at room temperature with 0.5 ng of ³²P-labelled oligonucleotide (50,000-100,000 cpm) in the presence or absence of unlabeled competitor after which the mixture is loaded on a
- 30 4% polyacrylamide gel prepared in 1X Tris borate/EDTA and electrophoresed at 200

V for 2 h. Following electrophoresis the gels are dried and exposed to film for detection of the binding reaction.

The effect of compounds on the phosphorylation of I κ B may be monitored in a Western blot. Cellular extracts are subjected to sodium dodecyl sulfate-

- 5 polyacrylamide gel electrophoresis (SDS-PAGE) on 10% gels (BioRad, Hercules, CA) and the proteins transferred to nitrocellulose sheets (Hybondtm-ECL, Amersham Corp., Arlington Heights, IL). Immunoblot assays are performed using a polyclonal rabbit antibody directed against I κ B α or I κ B β followed with a peroxidase-conjugated donkey anti-rabbit secondary antibody (Amersham Corp., Arlington Heights, IL). Immunoreactive bands are detected using the Enhanced Chemiluminescence (ECL) assay system (Amersham Corp., Arlington Heights, IL).

- Assays for I κ B kinases were conducted as follows: IKK- α was expressed as a hexa-histidine tagged protein in baculovirus-infected insect cells and purified over a Ni-NTA affinity column. Kinase activity was assayed using 50 ng of purified
- 15 protein in assay buffer (20 mM Hepes, pH 7.7, 2 mM MgCl₂, 1 mM MnCl₂, 10 mM β -glycerophosphate, 10 mM NaF, 10 mM PNPP, 0.3 mM Na₃VO₄, 1 mM benzamidine, 2 μ M PMSF, 10 μ g/ml aprotinin, 1 μ g/mL leupeptin, 1 μ g/mL pepstatin, 1mM DTT) containing various concentrations of compound or DMSO vehicle and ATP as indicated (Pharmacia Biotech Inc., Piscataway, NJ). The
- 20 reaction was started by the addition of 200 ng I κ B-GST (Santa Cruz Biotechnology, Inc., Santa Cruz, CA), in a total volume of 50 μ L. The reaction was allowed to proceed for 1 h. at 30 °C after which the reaction was terminated by the addition of EDTA to a final concentration of 20 mM. Kinase activity was determined by dissociation-enhanced lanthanide fluorescence immunoassay (Wallac Oy, Turku, Finland) using a phospho-I κ B- α (Ser32) antibody (New England Biolabs, Inc., Beverly, MA) and an Eu³⁺-labelled anti-rabbit IgG (Wallac Oy, Turku, Finland). The plates were read in a VICTOR 1420 Multilabel Counter (Wallac), using a standard europium protocol (excitation 340 nm, emission 615 nm; fluorescence measured for 400 μ s after a 400 μ sec delay). Data are expressed as fluorescence
- 25 (cps) units.
- 30

IKK- β was expressed as a GST-tagged protein, and its activity was assessed in a 96-well scintillation proximity assay (SPA). Briefly, IKK- β was diluted in assay buffer as described above (20 nM final), with various concentrations of compound or DMSO vehicle, 240 nM ATP and 200 nCi [γ - 33 P]-ATP (10 mCi/mL, 2000 Ci/mmol; NEN Life Science Products, Boston, MA). The reaction was started with the addition of a biotinylated peptide comprising amino acids 15 – 46 of I κ B- α (American Peptide) to a final concentration of 2.4 μ M, in a total volume of 50 μ L. The sample incubated for one hour at 30 $^{\circ}$ C, followed by the addition of 150 μ L of stop buffer (PBS w/o Ca $^{2+}$, Mg $^{2+}$, 0.1% Triton X-100 (v/v), 10 mM EDTA) containing 0.2 mg streptavidin-coated SPA PVT beads (Amersham Pharmacia Biotech, Piscataway, NJ). The sample was mixed, incubated for 10 min. at room temperature, centrifuged (1000 \times g, 2 minutes), and measured on a Hewlett-Packard TopCount.

The effect of IKK- β inhibitors on primary synovial fibroblast mediator production was assessed as follows: Primary cultures of human RSF were obtained by enzymatic digestion of synovium obtained from adult patients with rheumatoid arthritis as previously described (Roshak *et al.*, 1996b). Cells were cultured in Earl's Minimal Essential Medium (EMEM) which contained 10% fetal bovine serum (FBS), 100 units/ml penicillin and 100 μ g/ml streptomycin (GIBCO, Grand Island, NY), at 37 $^{\circ}$ C and 5% CO $_2$. Cultures were used at passages 4 through 9 in order to obtain a more uniform type B fibroblast population. For some studies, fibroblasts were plated at 5×10^4 cells/mL in 16 mm (diameter) 24 well plates (Costar, Cambridge, MA). Cells (70-80% confluence) were exposed to IL-1 β (1 ng/mL) (Genzyme, Cambridge, MA) for the designated time. Drugs in DMSO vehicle (1%) were added to the cell cultures 15 minutes prior to the addition of IL-1. Studies were conducted 3-4 times using synovial cells from different donors. RSF cellular extracts were prepared from cells treated as described above. Briefly, human RSF were removed by trypsin/EDTA, washed, and harvested by centrifugation. Cellular extracts were prepared as previously described (Dignam *et al.*, 1983; Osborn, *et al.*, 1989). Briefly, at the end of the incubation period the cells (1×10^7 cells) were washed 2x in PBS without Ca $^{2+}$ and Mg $^{2+}$. The resulting cell pellets were

resuspended in 20 μ L of Buffer A (10 mM Hepes (pH 7.9), 10 mM KCl, 1.5 mM $MgCl_2$, 0.5 mM.

Effect of IKK- β inhibition on human monocyte stimulated eicosanoid and cytokine production was assessed as follows: Monocytes were isolated from
5 heparinized whole blood by double gradient centrifugation as previously described. Isolated monocyte enriched PBMCs were then adhered to 24 well culture plates at 2×10^6 cells/mL in RPMI 1640 10% FBS (Hyclone, Logan, Utah) for 2 h. to further enrich the monocyte population. The media was then removed, cells washed once with RPMI 1640, and 1 mL RPMI 1640 10% FBS was added to the wells. Test
10 compounds are added to the wells with a final vehicle concentration of 0.05% DMSO. Monocytes were activated by the addition of 200 ng/mL endotoxin (LPS; *E. coli* serotype 026:B6)(Sigma, St. Louis, MO.) and incubated for 24 hrs. Cell-free supernates were analyzed by ELISA for TNF- α (EIA developed at SB), PGE₂ (Cayman Chemical, Ann Arbor, MI), and IL-8 and IL-6 Biosource International,
15 Camarillo, CA). Viability of the cells was determined by trypan blue exclusion.

Effect of IKK- β inhibitors on phorbol ester-induced inflammation was assessed as follows: The inflammatory response induced by the cutaneous application of phorbol ester (PMA) to the external pinnae of Balb/c mice has proven to be a useful model to examine multifactorial inflammatory cell infiltration and
20 inflammatory alteration of epidermis. The intense inflammatory lesion is dominated by neutrophil infiltration, which can be easily quantified by measurement tissue concentration myeloperoxidase, an azuriphilic granular enzyme present in neutrophils. In addition, the overall intensity of the inflammatory response can be measured by determination of ear thickness. Balb/c mice (n = 6/group) were
25 administered drug treatment or vehicle followed by PMA (4 μ g/ear). The mice were sacrificed 4 h. later, the ear thickness determined and NF- κ B activation was monitored by IkB α western or EMSA analysis.

Effect of IKK- β inhibitors on rat carrageenan-induced paw edema was assessed as follows: Male Lewis rats (Charles River- Raleigh, NC) were housed and
30 allowed free access to food and water, and weighed between 200-275g for each experiment. Compound or vehicle (0.5% Tragacanth (p.o.) or 10%DMSO,

- 5%DMA, 30% Cremophor(i.p.)) was administered 30 minutes to 1 hour prior to the carrageenan injection. Edema was induced by injection of 1% carrageenan in sterile dH₂O (0.05ml/paw) into the plantar surface of the right hindpaw. Paw thickness was measured prior to administration of compound or vehicle, and again at 3 hours, to determine change in paw volume. Rats were euthanized by CO₂ inhalation and the right hindfoot was removed, immediately frozen in liquid nitrogen and stored at -80C for analysis.

General

- Nuclear magnetic resonance spectra were recorded at either 250, 300 or 400 MHz using, respectively, a Bruker AM 250, Bruker ARX 300 or Bruker AC 400 spectrometer. CDCl₃ is deuteriochloroform, DMSO-d₆ is hexadeuteriodimethylsulfoxide, and CD₃OD is tetradeuteriomethanol. Chemical shifts are reported in parts per million (δ) downfield from the internal standard tetramethylsilane. Abbreviations for NMR data are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets, app = apparent, br = broad. J indicates the NMR coupling constant measured in Hertz. Continuous wave infrared (IR) spectra were recorded on a Perkin-Elmer 683 infrared spectrometer, and Fourier transform infrared (FTIR) spectra were recorded on a Nicolet Impact 400 D infrared spectrometer. IR and FTIR spectra were recorded in transmission mode, and band positions are reported in inverse wavenumbers (cm⁻¹). Mass spectra were taken on either VG 70 FE, PE Syx API III, or VG ZAB HF instruments, using fast atom bombardment (FAB) or electrospray (ES) ionization techniques. Elemental analyses were obtained using a Perkin-Elmer 240C elemental analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. All temperatures are reported in degrees Celsius.

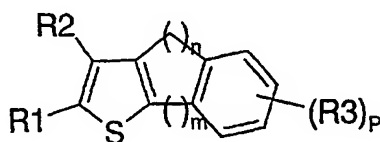
Analtech Silica Gel GF and E. Merck Silica Gel 60 F-254 thin layer plates were used for thin layer chromatography. Both flash and gravity chromatography were carried out on E. Merck Kieselgel 60 (230-400 mesh) silica gel.

- Where indicated, certain of the materials were purchased from the Aldrich Chemical Co., Milwaukee, Wisconsin, TCI America, Portland, OR..

- 5 The above description fully discloses the invention including preferred
embodiments thereof. Modifications and improvements of the embodiments
specifically disclosed herein are within the scope of the following claims. Without
further elaboration, it is believed that one skilled in the art can, using the preceding
description, utilize the present invention to its fullest extent. Therefore the
10 Examples herein are to be construed as merely illustrative and not a limitation of the
scope of the present invention in any way. The embodiments of the invention in
which an exclusive property or privilege is claimed are defined as follows.

What is claimed is:

1. A compound according to formula (I) hereinbelow:



(I)

5

wherein:

R₁ represents NR₄R₅;

R₂ represents CONH₂ or SO₂NH₂;

- 10 R₃ is selected from the group consisting of halogen, C₁₋₄alkyl, NH₂, CF₃, OCF₃,
O-alkyl, S-alkyl, CN, CHO, SO₂-alkyl, and NO₂;

R₄ represents C₁₋₄alkyl;

R₅ represents CONHR₆;

R₆ is selected from the group consisting of hydrogen, alkyl and aryl;

m is 0 or 1;

- 15 n is 1 or 2; and

p is 1, 2 or 3.

2. A compound according to claim 1 wherein the compound is selected from
the group consisting of:

- 2-Amino-4H-indeno[1,2b]thiophene-3-carboxylic acid amide;
20 2-Ureido-4H-indeno[1,2b]thiophene-3-carboxylic acid amide;
2-Amino-4,5-dihydro-naphtho[2,1-b]thiophene-3-carboxylic acid amide; and
2-Ureido-4,5-dihydro-naphtho[2,1-b]thiophene-3-carboxylic acid amide.

3. A method of treating a disease characterized by pathological NF-κB
25 activation comprising inhibiting the pathological activation by administering to a
patient in need thereof an effective amount of a compound according to claim 1.

4. A method according to claim 3 wherein the disease is an inflammatory or tissue repair disorder.
5. A method according to Claim 4 wherein the disease is selected from the group consisting of inflammatory and tissue repair disorders, particularly rheumatoid arthritis, inflammatory bowel disease, asthma and COPD (chronic obstructive pulmonary disease) osteoarthritis, osteoporosis and fibrotic diseases, dermatosis, including psoriasis, atopic dermatitis and ultraviolet radiation (UV)-induced skin damage, autoimmune diseases including systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, ankylosing spondylitis, tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, cancer, including Hodgkins disease, cachexia, inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS), adult respiratory distress syndrome, and Ataxia Telangiectasia.
6. A method according to Claim 3 wherein said disease is dermatosis.
7. A method according to Claim 3 wherein the disease is selected from the group consisting of: psoriasis, atopic dermatitis, and UV-induced skin damage.
8. A method according to Claim 3 wherein the disease is selected from the group consisting of autoimmune diseases; tissue and organ rejection, Alzheimer's disease, stroke, atherosclerosis, restenosis, diabetes, glomerulonephritis, osteoarthritis, osteoporosis, and Ataxia Telangiectasia.
9. A method according to Claim 3 wherein said disease is an autoimmune disease.
10. A method according to Claim 3 wherein the autoimmune disease is systemic lupus erythematosus, multiple sclerosis, psoriatic arthritis, or ankylosing spondylitis, diabetes

11. A method according to any one of Claim 1 wherein the disease is cancer and or cachexia.
- 5 12. A method according to Claim 3 wherein the cancer is Hodgkins disease.
13. A method according to Claim 3 wherein the disease is inflammation associated with infection and certain viral infections, including acquired immune deficiency syndrome (AIDS).
- 10 14. A method according to Claim 3 wherein the disease is AIDS.
15. A method according to Claim 3 wherein the disease is adult respiratory distress syndrome.
- 15 16. A method according to claim 3 wherein there is dual inhibition of NF- κ B and checkpoint kinase.

ABSTRACT OF THE INVENTION

The present invention provides novel compounds and methods for using
5 them to treat diseases with aminothiophene inhibitors of IKK- β phosphorylation of
I κ B. In so doing these aminothiophene inhibitors block pathological activation of
transcription factor NF- κ B in which diseases excessive activation of NF- κ B is
implicated.

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